THE HEART AND HYPERTENSION

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University Hospital
Bordeaux
INCREASED LVM

• Cardiomyocytes hypertrophy is a response to pressure overload
• This response is influenced by many factors and genes
• It has long been viewed as an adaptative process to normalize wall stress and restore heart muscle economy. But this view is now seriously challenged
• Increased LVM is not muscle only
INCREASED LVM

• HYPERTROPHY
  – Requires mechanical stress
  – Modulated by non mechanical factors
    • Hormones
    • Salt
    • Genes
  – May show regression within weeks

• FIBROSIS (>6%, up to 30%)
  – Independent of mechanical stress
  – Influence of
    • All
    • Aldosterone
    • ?
  – Regression may require months
MISE EN EVIDENCE HVG

• ECG
  – Voltage
    • Sokolow: Sv1+Rv5 or Rv6 > 35(8) mm
    • Cornell: RavL + Sv3 + 8 mm(F)> 28
  – Cornell Voltage* durée QRS>2440
  – Troubles de repolarisation

• ECHO
  – M mode
  – 2D, 3D

• IRM

• BNP?
2D guided M Mode recording of LV parasternal view

Septal Thickness (ST)

End Diastolic Diameter (EDD)

Posterior Wall Thickness (PWT)
HOW TO READ M MODE RECORDINGS?
LIMITS LINKED TO GEOMETRY HYPOTHESIS

LVM = 1.04((EDD + ST + PWT)^3 - EDD^3) - 13.6

- WALL MOTION ABNORMALITIES
- ASYMMETRIC HYPERTROPHY
- LV DILATATION
  - do not calculate if EDD > 60mm
## REPRODUCIBILITY

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Patients</th>
<th>n</th>
<th>SDD</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOSSE 1983</td>
<td>Misc</td>
<td>20</td>
<td>40g</td>
<td>15.6%</td>
</tr>
<tr>
<td>DEVEREUX 1984</td>
<td>Normal</td>
<td>89</td>
<td>29g</td>
<td></td>
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<tr>
<td>GOTTDIENER 1995</td>
<td>HT</td>
<td>96</td>
<td>27g</td>
<td>8.3%</td>
</tr>
<tr>
<td>GOSSE 1995</td>
<td>HT</td>
<td>47</td>
<td>32g</td>
<td>14.6%</td>
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<tr>
<td>GOSSE (PICXEL) 2004</td>
<td>HT</td>
<td>210</td>
<td>33-44g</td>
<td>13-17%</td>
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</tbody>
</table>
LVH CUT OFF

• INDEXATION FOR LVM
  - BSA
  - Height
  - Height\(^{2.7}\)

• Gender influence

• Influence of physical training?

• Cut off, usually based on 95\(^{th}\) percentile in normal subjects
  • M:125-130 g/m\(^2\), F:110g/m\(^2\)
  • M: 50 g/m\(^{2.7}\), F:47 g/m\(^{2.7}\)
CUTOFF For prediction of CVE

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CVE</th>
<th>cut off</th>
<th>Sens</th>
<th>Spé</th>
<th>AUC</th>
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<tbody>
<tr>
<td>BX cohort</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>M+F (637)</td>
<td>95</td>
<td>52g/m².7</td>
<td>78%</td>
<td>51%</td>
<td>0.69</td>
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<tr>
<td>M (395)</td>
<td>70</td>
<td>55g/m².7</td>
<td>71%</td>
<td>53%</td>
<td>0.66</td>
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<tr>
<td>F (242)</td>
<td>25</td>
<td>47g/m².7</td>
<td>88%</td>
<td>51%</td>
<td>0.72</td>
</tr>
<tr>
<td>ARIC Black (57%HT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nunez, Hypertension 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M (570)+F (1046)</td>
<td>192</td>
<td>51g/m².7</td>
<td>53%</td>
<td>62%</td>
<td></td>
</tr>
</tbody>
</table>
LVH PREVALENCE

Bordeaux cohort of never treated hypertensives

\((n=500)\)

- **ECG**
  - SOKOLOW > 35 mm: 6\%, > 38mm: 3\%
  - CORNELL product > 2440: 10\%
  - ECG LIFE: 12\%

- **M mode ECHO**
  - g/m^2: M 134, F 110: 36\%
  - g/m^{2.7}: M 53, F 47: 51\%
# Remodelage Ventriculaire Gauche dans L'HTA

## Normal
- $h=10\ mm$
- $r=25\ mm$
- $h/r=0.4$
- $MVG=213\ g$

## Concentrique
- $h=14\ mm$
- $r=22.5\ mm$
- $h/r=0.62$
- $MVG=296\ g$

## Excentrique
- $h=10\ mm$
- $r=30\ mm$
- $h/r=0.33$
- $MVG=294\ g$
REMODELAGE VG DANS HTA

- HVG CONCENTRIQUE: $\uparrow$MVG, $\uparrow$H/R: 8%
- HVG EXCENTRIQUE: $\uparrow$MVG, H/R=↓: 27%
- REMODELAGE CONCENTRIQUE: $\uparrow$H/R, MVG Nale: 13%
- VG NORMAL: 52%

GANAU, JACC 1992, 19:1550-1558
THE CASE AGAINST THE VALIDITY OF WALL-STRESS HYPOTHESIS

• LVH IS A STRONG AND INDEPENDENT RISK FACTOR WITH A CONTINUOUS RELATIONSHIP BETWEEN LVM AND RISK

• SYSTOLIC FUNCTION IS OFTEN IMPAIRED DESPITE NORMAL REST EJECTION FRACTION
  – MIDWALL FRACTIONNAL SHORTENING
  – SPECKLE TRACKING

• LEFT VENTRICULAR FILLING IS IMPAIRED
  – RELAXATION
  – COMPLIANCE

• CORONARY PERFUSION IS OFTEN IMPAIRED IN HYPERTENSION

• EXPERIMENTAL DATA SHOW THAT CARDIAC HYPERTROPHY IS NOT AN ADAPTATIVE RESPONSE
4 year age-adjusted incidence (/100 pts) of cardiovascular disease according to LVM/h (Framingham)

Levy, NEJM 1990, 322:1561-1566
PIUMA STUDY
Schillaci, Hypertension 2000, 35: 580-586

1925 HT, mean FU: 4±2 years, 181 CV events
Age, sex and BP adjusted event free survivals curves for LVM/h^{2.7} quintiles in Bordeaux cohort

n=719
Mean follow-up= 136±65 months
99 CV events
LVH: MARKER OF RISK

⇒ INFLUENCED BY SEVERAL RISK FACTORS: Age, gender, BP(central), Blood viscosity, overweight, alcool, salt, cholesterol?....

⇒ INTEGRATES THEIR VARIATIONS WITH TIME
LVM as a witness of BP over time
Inappropriate LVH

LVM

ADVERSE EFFECTS
• ISCHIEMIA
• IMPAIRED FILLING
• ARRYTHMIAS

ADVERSE EFFECTS
• IMPAIRED SYSTOLIC FUNCTION

STROKE WORK
Prognostic impact of inappropriate LVM in hypertension: the MAVI study

*de Simone, Hypertension 2002, 40:470*

CV event free survival curves at mean of covariates (age, sex, BMI, SBP...) according to LVM

Predicted LVM = 55.37 + 6.64height^{2.7} + 0.64SW - 18.07gender

SW = SBP * Stroke volume

![Graph showing event-free survival curves at mean of covariates (age, sex, BMI, SBP...) according to LVM. Curves are labeled as follows: low LV mass, appropriate LV mass, and inappropriate LV mass. The graph indicates a significant difference between the curves at p<0.02.](image)
HYPERTENSION = PATHOLOGIC LVH

• IMPAIRED CORONARY RESERVE
  – WHY?
    • vascular remodeling
    • Impaired endothelial function
    • Capillaries rarefaction
    • Increase aortic stiffness and reduced perfusion pressure
  – CONSEQUENCES
    • Unbalanced offer and demand
    • Ischemic heart disease
      – Impaired relaxation and LV filling
      – Impaired systolic function
HYPERTENSION = PATHOLOGIC LVH

- IMPORTANCE OF FIBROSIS
  Diez (circulation 2002:2512-2517)
  • 34 HT with LVH, transvenous endomyocardial biopsies for assessment of Collagen Volume Fraction and pulsed doppler mitral flow
  • Correlation between CVF and reduced deceleration time of early mitral filling wave

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![](image)
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THE LEVER EFFECT OF MYOCARDIAL FIBERS ORGANISATION

• 15% fiber shortening along the long axis leads to only an 8% increase in myocyte diameter. Yet, 40% radial LV wall thickening and 60% ejection fraction are typically observed.

• Myocardial fibers are grouped into lamina (sheets) 3*4 cells thick interconnected by extracellular matrix

• Radial and longitudinal shear of these sheets play a role of lever to increase wall thickening
Wall Thickening Mechanism

\[ E_{33} = E_{ss} \cos^2 \beta + E_{nn} \sin^2 \beta + 2E_{sn} \sin \beta \cos \beta \]
Fibrosis and systolic function?

- Even small changes in the initial sheet angle may have large effects on wall thickening.
- Pathological changes in macrostructure of the ventricular wall may influence sheet motion and, therefore, wall thickening and synchronicity.
REDUCTION DU STRAIN LONGITUDINAL DANS HTA

• Retrouvée dans plusieurs études comparant HTA et sujets normaux mais aussi HTA et athlètes

• Une étude négative (Narayanan, Circulation 2009)

• Lien possible avec degré d’HVG et fibrose
  – Poulsen Heart 2005, 91:624-9
## HTA Maligne (n=25)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-3 mois</th>
<th>11± 14 mois</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>PAS (mmHg)</strong></td>
<td>163±18</td>
<td>126±14</td>
<td>129±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PAD (mmHg)</strong></td>
<td>97±13</td>
<td>80±9</td>
<td>81±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cornell Product</strong></td>
<td>2609±822</td>
<td>2179±934</td>
<td>1783±762</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>creatinine</td>
<td>145±79</td>
<td>130±53</td>
<td>115±33</td>
<td>0.06</td>
</tr>
<tr>
<td>MVG/t².⁷</td>
<td>76±23</td>
<td>58±18</td>
<td>51±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FE (%)</strong></td>
<td>50±12</td>
<td>55±10</td>
<td>58±11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>FE&lt;40, n=</strong></td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>GLS</strong></td>
<td>12.3±3.8</td>
<td>15.0±4.3</td>
<td>17.2±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>GLS&lt;12.8 n=</strong></td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Fonction diastolique

• Apport du strain radial diastolique :
  – Association aux paramètres classiques de fonction diastolique
  – Mais moins bonne sensibilité
• Indices de dysfonction diastolique détectés par strain longitudinal avant le stade de DD « globale »
REDUCTION VITESSE DETORSION DANS HTA

• REFLET DEL’EFFICACITE DE LA RELAXATION
  – Mu, Echocardiography, 2010, 27:146-54
Asynchronisme

• Rôle continu de l’asynchronisme dans la dégradation de la fonction myocardique
• Phénomène mis en évidence dans 2 études, et associé à la présence d’une HVG et d’une dysfonction diastolique symptomatique

- Genetically altered mice unable to develop LVH
- Transverse aortic constriction to increase afterload
- Despite high parietal stress these mice showed significantly less deterioration in cardiac function than the wild type banded mice developing LVH

![Graph showing LV midwall end systolic stress and fractional shortening over time](image-url)
ANTIHYPERTENSIVE TREATMENT REDUCES LVH

• MANY STUDIES BUT OFTEN WITH FEW PATIENTS, SHORT DURATION

• ALL DRUGS ARE EFFICIENT WITH THE EXCEPTION OF MINOXIDIL AND HYDRALAZINE

• POOR CORRELATIONS BETWEEN BP AND LVM REDUCTIONS: IS THERE A SPECIFIC DRUG ACTION??
IS THERE A SPECIFIC DRUG ACTION ON LVH??

• COMPARATIVE STUDIES EXIST BUT FEW SHOW SUFFICIENT POWER

• META-ANALYSIS SHOW GREATER EFFICACY OF ARAII and ACE INHIBITORS VERSUS β BLOCKERS AND DIURETICS BUT
  – Many studies of poor quality
  – Diuretics often added to ACE inhibitors and ARAII
  – Publication bias

• WE NEED WELL DESIGNED AND POWERFULL COMPARATIVE STUDIES
LVH Régression Meta-analysis

Klingbeil: 80 studies / Dahlöf: 109 studies

Régression

Progression

Diurétics

β-Blockers

ACEI

Calcium antagonist

ARAII


Dahlöf B: Am J Hypertens. 1992;5:95-110
OPTIMAL TRIAL DESIGN FEATURES
Devereux, Dahlof: J Human Hypertens 1994, 8:735-9

- ADEQUATE GENDER, AGE AND ETHNIC MIX
- DOUBLE BLIND, RANDOMISED COMPARATIVE TRIAL
- ADEQUATE SAMPLE SIZE (150-200/Gp with echo)
- ADEQUATE DURATION: >= 1 YEAR
- CENTRAL BLIND MEASUREMENT OF LVM BY TRAINED ECHOCARDIOGRAPHISTS
RECOMMANDATIONS FOR MULTICENTRIC LVH REGRESSION TRIALS
Gosse J; Hypertens 2003, 21:217-221

- CENTRALIZED CONTROL OF INCLUSION CRITERIA
- CENTRALIZED CONTROL OF QUALITY FOR ALL RECORDINGS
- FINAL CENTRALIZED READING
  - BLIND TO TREATMENT AND temporal SEQUENCE
  - ALL TRACINGS OF THE SAME Pt READ BY THE SAME READER
  - ALL TRACINGS MIXED TOGETHER
- 2 INITIAL ECHO separated by a 2-4 weeks placebo run-in
  - SDD as an OVERALL QUALITY INDICE
  - QUANTIFICATION OF REGRESSION TO THE MEAN
# MAIN ECHO STUDIES ON LVH REGRESSION

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Drugs</th>
<th>LVMI g/m²</th>
<th>BP mmHg</th>
<th>Duration (weeks)</th>
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</thead>
<tbody>
<tr>
<td>LIFE</td>
<td>825</td>
<td>Los Vs Aten (+Htz in 90%)</td>
<td>-22±22</td>
<td>-30/-16</td>
<td>240</td>
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<td></td>
<td></td>
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<td>-18±20*</td>
<td>-29/-16</td>
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<tr>
<td>PICXEL</td>
<td>679</td>
<td>Per/ind Vs Ena</td>
<td>-14±24</td>
<td>-22/-10</td>
<td>52</td>
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<tr>
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<td></td>
<td></td>
<td>-4±24*</td>
<td>-18/-8*</td>
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<tr>
<td>LIVE</td>
<td>411</td>
<td>Ind Vs Ena (+prazosin in 20%)</td>
<td>-8±30</td>
<td>-25/-13</td>
<td>48</td>
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<td></td>
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<td>-2±28*</td>
<td>-25/-12</td>
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<tr>
<td>CATCH</td>
<td>196</td>
<td>Cande Vs Ena (+Htz in 47-54%)</td>
<td>-15±23</td>
<td>-27/-16</td>
<td>48</td>
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<tr>
<td></td>
<td></td>
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<td>-13±23</td>
<td>-26/-16</td>
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<tr>
<td>PRESERVE</td>
<td>235</td>
<td>Ena Vs Nife (+Htz in 34-59%)</td>
<td>-15±21</td>
<td>-22/12</td>
<td>48</td>
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<tr>
<td></td>
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<td>-17±18</td>
<td>-21/13</td>
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<tr>
<td>REGAAL</td>
<td>219</td>
<td>Los Vs Aten (+Htz in 86-78%)</td>
<td>-7±20</td>
<td>-24/-11</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-4±21</td>
<td>-24/-14</td>
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</tr>
</tbody>
</table>
LIFE

Change from Baseline in LVH Regression

Cornell Product

Mean change from baseline (%)

-18 -16 -14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16 18

Losartan: 10.2 %, p<0.0001

Atenolol: 4.4 %

Sokolow-Lyon

Mean change from baseline (%)

-18 -16 -14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16 18

Losartan: 15.3 %, p<0.0001

Atenolol: 9.0 %

Stroke

Losartan

Atenolol
LIFE: ECHO RESULTS

n=878
LVH REGRESSION IMPROVES OUTCOME
(Verdecchia AJH, 2003:16:895-899)

- Meta analysis of small cohorts
  (Verdecchia AJH, 2003:16:895-899)
- LIFE STUDY
  (Devereux, JAMA 2004,292:2350-6)

LVM seems to be a good surrogate end point
MVG critère intermédiaire ?

- L’augmentation de la MVG est associée à un risque accru de complications
- La diminution de la MVG est associée à une réduction du risque
- La correlation entre risque et MVG existe dans toutes les populations
- Il y a un strict parallelisme entre l’évolution de la MVG et du risque ??
MAIS EN PRATIQUE??
LVM assessment in hypertensive patient. When?

- LVM seems to be a good surrogate end point
- But
  - ECG is not sensitive enough
  - echo assessment of LVM shows insufficient reproducibility
  - MRI cannot be proposed for routine evaluation
  - No study demonstrates the cost effectiveness of systematic LVM assessment
Impact of baseline echo on treatment outcome in primary care patients with newly detected hypertension
Martina et Al, AJH, 2006, 19:1150-5

• 177 Ht avec échocardiographie randomisés:
  – Résultats écho communiqués au médecin
  – Résultats écho NON communiqués au médecin

<table>
<thead>
<tr>
<th>Table 3.</th>
<th>Left ventricular mass index (g/m²), mean office, and 24-h ambulatory blood pressure (mm Hg) after 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Echo group</td>
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<tr>
<td>Left ventricular mass index</td>
<td>106 ± 21</td>
</tr>
<tr>
<td>Prevalent concentric geometry‡ (%)</td>
<td>69</td>
</tr>
<tr>
<td>Systolic office blood pressure (mm Hg)</td>
<td>141 ± 15</td>
</tr>
<tr>
<td>Diastolic office blood pressure (mm Hg)</td>
<td>88 ± 10</td>
</tr>
<tr>
<td>Mean 24-h systolic blood pressure (mm Hg)</td>
<td>133 ± 12</td>
</tr>
<tr>
<td>Mean 24-h diastolic blood pressure (mm Hg)</td>
<td>83 ± 7</td>
</tr>
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</table>

* After adjustment for differences in baseline left ventricular mass index; † After adjustment for differences in baseline blood pressure; ‡ 2x end-diastolic posterior wall thickness/end-diastolic LV internal diameter ≥ 0.43.
CRITERES FONCTIONNELS?

• Remplissage:
  – Flux mitral (E, E/A)
  – DTI (E’)

• FONCTION SYSTOLIQUE
  – FS
  – FE
  – Fonction systolique a mi paroi
Does Information on Systolic and Diastolic Function Improve Prediction of a Cardiovascular Event by Left Ventricular Hypertrophy in Arterial Hypertension?

Giovanni de Simone, Raffaele Izzo, Marcello Chinali, Marina De Marco, Giuseppina Casalnuovo, Francesco Rozza, Daniela Girfoglio, Gianni Luigi Iovino, Bruno Trimarco, Nicola De Luca

*Hypertension. 2010;56:99-104.*
INDICATIONS ECHO DANS HTA?

• INDICATION PEU DISCUTABLES
  – HTA SYMPTOMATIQUE
  – ANOMALIES ECG, Rx

• INDICATIONS DISCUTABLES
  – ECHO INITIAL D'EVALUATION DU RISQUE
  – HTA LEGERE OU LIMITE POUR INDICATION TTT
  – HTA REFRACTAIRE

• PAS D'INDICATION
  – SURVEILLANCE EVOLUTION HVG
ECG

NORMAL
Dont eliminate LVH

LOW RISK
ECHO USELESS IF ASYMPTOMATIC

HIGH RISK
ECHO TO ASSESS LV function??

Abnormal
REPOLARISATION
VERY HIGH RISK

LVH

Normal
REPOLARISATION
HIGH RISK
ECHO

Look for ischemic heart disease
ECHO

ECHO?
Better assessment of risk but cost/effectiveness unknown